World Intellectual Property Organization
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification[5] **C07D 453/02, A61K 31/435**	**A1**	**(11) International Publication Number**	**WO 90/14347**
		(43) International Publication Date	**29 November 1990 (29.11.90)**

(21) International Application Number
PCT/JP90/00645

(22) International Filing Date 22 May 1990 (22.05.90)

(30) Priority Data Application Number 1989/130899
24 May 1989 (24.05.89) JP

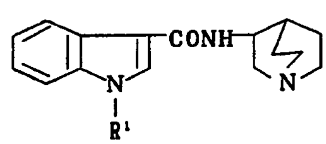
(71) Applicant (*for all designated states except US*)
Nippon Shinyaku Co., Ltd [JP/JP]
14 Nishinosho-Monguchi-cho, Kisshoin, Minami-ku, Kyoto 601 (JP)
(72) Inventor and
(75) Inventor/Applicant (*US only*)
KIMURA Kiyoshi [JP/JP]
5-55-21 Yasuokaji-cho, Takatsuki-shi, Osaka 569
KISE Masahiro [JP/JP]
123-1-2 Sanjo-Noboru Fukunaga-cho
Tomi-kojiro-dori, Chu-kyo-ku, Kyoto 601
KITANO Masahiko [JP/JP]
9-4 Matsugesaki, Donoue-cho
Sakyo-ku, Kyoto 606
UKAI Yojiro [JP/JP]
171-9 Noro-machi, Kusatsu-shi, Shiga 525
OGAWA Kazuhiro [JP/JP]
1-26-106 Kusenaka, Kuse-cho
Minami-ku, Kyoto 601
FUKUI Takako [JP/JP]
3 Otowa-Inashiba, Yamashina-ku, Kyoto 607

(74) Agent
KATAOKA, Hiroshi et al.
Nippon Shinyaku Co., Ltd.
14 Nishinosho-Monguchi-cho
Minami-ku, Kyoto 601

(81) Designated States
AT (European Patent), AT, AU, BE (European Patent), CA, CH (European Patent), CH, DE (European Patent)* DK (European Patent), DK ES (European Patent), FI, FR (European Patent), GB (European Patent), GB, HU, IT (European Patent), JP, KR, LU (European Patent), NL (European Patent), NL, NO, SE (European Patent), SE, SU, US

Published
With international search report

(54) Title: INDOLE DERIVATIVES AND MEDICINE



(I)

(57) Abstract

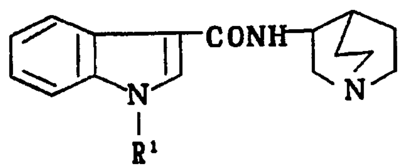
Indolecarboxamide derivatives of general formula (1) and a serotonin antagonist mainly comprising the same. The test on the activity of the compounds (1) in the inhibition of Bezold-Jarisch reflex has proved that the activity is 3 to 5 times as potent as those of the conventional drugs and also the duration of action is 5 to 10 times as long as those of the conventional ones. The test on the activity of the same in the inhibition of cisplatin-induced vomiting has also proved that this activity is potent. Since the compounds of the invention have only a low acute toxicity, they are very useful as a serotonin antagonist.

SPECIFICATION

Indole Derivatives and Medicine

Technical Field

The present invention concerns indole carboxamide derivatives and their pharmacologically acceptable salts represented by General Formula [I] below (wherein, R^1 represents a hydrogen or alkyl group).



[I]

The compounds set forth in this invention exhibit serotonin antagonism and are useful as an antiemetic agent, agent for regulating gastrointestinal peristalsis, agent for the treatment of migraine headaches, antipsychotic agent, antianxiety agent and the like.

Background Technology

Serotonin (5-HT) is a neurotransmitter that is widely distributed throughout the body and has an extremely large variety of physiological actions. Serotonin receptors are thought to exist in 3 subtypes: 5-HT_1, 5-HT_2 and 5-HT_3.

Known functions of the 5-HT_3 receptor are to promote release of neurotransmitters (noradrenaline, acetylcholine) from neurons, to depolarize sympathetic and parasympathetic nerve ganglions, and to induce reactive bradycardia and pain. However, many functions of the 5-HT_3 receptors are not understood, and the antiemetic action of their antagonists and the mechanism by which they express their neurotropic effect have not been elucidated at this point.

The 5-HT_3-specific antagonist GR-38032F (Ondansetron) strongly inhibits vomiting during the administration of anticancer agents, and it is said to exhibit excellent antianxiety and antipsychotic effects and the like.

Various types of indole derivatives having an azabicyclo group have been reported (i.e., JP 63-277622A, JP63-277623A, JP62-116580A, ICS-205-930/JP61-212521A, etc.)

However, an indole-3-carboxamide derivative having a hydrogen atom or alkyl group substituent at the No. 1 position of the indole skeleton and having a quinuclidinyl (1-azabicyclo-[2,2,2]-oct-3-yl) group at the No. 3 position has not been reported in the literature.

Although it may be possible to assert that the inventive compounds can be expressed by combining the substituents of the compounds described in the claims of the above patents, the compounds themselves are not disclosed in any of the above specifications, and therefore the inventive compounds set forth herein are not described in the above documents.

Disclosure of the Invention

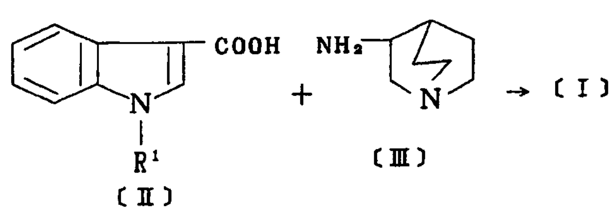
The inventors conducted research to obtain a compound with efficacy, safety and sustained action that is superior to the serotonin antagonists known in prior art. The object of this invention, therefore, is to obtain a novel compound having serotonin antagonism.

The essential constitution of the present invention lies in the structure per se of the compound represented in General Formula [I]. The compounds set forth in this invention are not only novel compounds that have not been described in the literature, but as shown below, have excellent pharmacological action and low toxicity.

Most Preferred Embodiment of the Invention

A straight chain or branched alkyl group of 1-4 carbons is preferred as the alkyl group represented as R^1 in General Formula [I], and examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, etc.

The inventive compounds can be produced by the process described below.



In these formulas, R1 is the same as above.

An indole-3-carboxylic acid [II] or its reactive derivative is reacted with a quinuclidyl [sic, quinuclidinyl?] amine [III] to produce the compound of [I].

This amidation reaction itself can be performed by publicly known methods.

For example, the method in which a reactive derivative of [II], i.e., an acid halide (for example, an acid chloride, acid bromide and the like) is suitably reacted with a lower alkyl ester or active ester (for example, p-nitrophenyl ester, p-nitrobenzyl ester, p-chlorophenyl ester, 1-hydroxybenzotriazole ester and the like), imidazolide or mixed acid anhydride (for example, a mixed acid anhydride of lower alkyl carbonic acids, mixed acid anhydride of lower alkyl phosphoric acids) and the like, or a method in which [II] and [III] are directly bonded using a condensation agent, and the like.

When an acid halide is used, normally the halide of [II] and [III] are reacted in the presence of a base at –20 to 30°C in a solvent that is inert in the reaction. Examples of solvents include ether type solvents such as ether, tetrahydrofuran, dioxin and the like; halogenated hydrocarbon type solvents such as methylene chloride, chloroform, and the like; hydrocarbon type solvents such as benzene, toluene, xylene and the like; pyridine; water; or mixtures thereof.

Examples of the base include inorganic bases such as potassium carbonate, sodium hydroxide, potassium hydroxide and the like, and organic tertiary amine bases such as pyridine, triethylamine, tributylamine, dimethylaniline and the like.

The reaction time will vary depending on the starting materials, base used, and type of solvent, but normally 30 hr to 12 hr is appropriate.

The preferred amount is normally 1 to 1.2 moles of acid halide to 1 mole of [III].

When direct bonding is performed using a condensing agent, normally [II] and [III] are reacted in the presence of the condensing agent at –20 to 80°C in a solvent that is inert in the reaction. The aforementioned solvents can be used as the solvent.

Examples of the condensing agent include carbodiimides such as dicyclohexyl carbodiimide and the like, quaternary pyridinium salts such as 2-chloro-N-methylpyridinium iodide or 2-methanesulfonyloxy-N-methylpyridinium iodide and the like, and diphenyl phosphoryl azide and the like.

Starting material [II] can be produced as shown in the Reference Example.

The inventive compounds obviously have asymmetric carbon atoms. Therefore, D- and L-optically active forms exist, and the scope of the present invention includes each optical isomer and racemic mixtures thereof.

The optical isomers can be obtained from the racemic mixtures that were obtained in the above manner by performing optical separation with publicly known methods that use an optically active acid (tartaric acid, dibenzoyl tartaric acid, mandelic acid, 10-camphorsulfonic acid and the like) to take advantage of the different basic properties of the isomers, by chromatography and the like, by a combination thereof, or by using a previously prepared optically active compound [III] as a starting material.

The target compound [I] prepared in this manner may be separated and purified by publicly known methods in the form of a free salt or acid addition salt, and by processes such as concentration, liquid transformation, solvent transfer, solvent extraction, crystallization, fractional distillation, chromatography and the like.

Acid addition salts include the salts of mineral acids such a hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and the salts of organic acids such as acetic acid, oxalic acid, citric acid, tartaric acid, maleic acid, succinic acid, fumaric acid, p-toluenesulfonic acid, benzenesulfonic acid, methanesulfonic acid and the like.

When the inventive compound is administered as a medicine, the inventive compound may be administered to animals including humans as is or in a medicinal composition containing, for example, 0.1-99.5%, preferably 0.5-90%, of the inventive compound in a pharmaceutically acceptable nontoxic, inert vehicle.

One or more solid, semisolid or liquid diluents, fillers or other pharmaceutical excipients can be used as the vehicle. Preferably the medicinal composition will be administered in the form of dose units. The inventive medicinal compound can be administered intravenously, orally, interstitially, locally (percutaneously and the like) or rectally. Naturally, a dosage form suitable to the route of administration should be used. Oral and intravenous administrations are especially preferred.

The dose of the antiemetic agent should be adjusted in consideration of the characteristics of the patient such as age, body weight and the like, route of administration, nature and seriousness of

the disease and the like, but normally for adults a daily dose of the inventive compound as active ingredient will be in the range of 0.1-100 mg/person, preferably 0.1-10 mg/person orally, or 0.001-10 mg/person intravenously.

Depending on the circumstances, a smaller dose may suffice or a larger dose may be needed. The daily dose may also be divided into 2-4 portions.

EXAMPLES

The present invention is described below in greater detail through the use of Reference Examples, Examples, and Test Examples concerning the inventive compound.

REFERENCE EXAMPLE 1

<u>1-methylindole-3-carboxylic acid</u>

A suspension of 2.7 g of 60% NaH in 20 mL of N,N-dimethylformamide was prepared, and with stirring at 0°C, a solution of 5.0 g indole-3-carboxylic acid in 30 mL of N,N-dimethylformamide was dripped in. After stirring for 1 hr at 0°C, 8.6 g of dimethyl sulfate was dripped in and stirred for 2.5 hr at room temperature. After ammonia water was added to the reaction solution, extraction with chloroform was performed followed by dehydration with anhydrous magnesium sulfate, filtration, and then the chloroform was distilled off under vacuum. A mixture of n-hexane and isopropyl ether was added to the residue, crystals were precipitated, filtered, and rinsed with n-hexane to obtain 3.3 g of the methyl ester of 1-methylindole-3-carboxylic acid as white crystals.

To this was added 35 mL of 10% sodium hydroxide solution and 150 mL of methanol, and the solution was heated and refluxed for 24 hr. After cooling, 10% HCl was added to neutralize the reaction mixture, and the precipitated crystals were filtered and rinsed with water to obtain 2.5 g of 1-methyindole-3-carboxylic acid as white crystals.
Melting point 216°C.

REFERENCE EXAMPLE 2

<u>1-ethylindole-3-carboxylic acid</u>

A suspension of 2.7 g of 60% NaH in 30 mL of N,N-dimethylformamide was prepared, and with stirring at 0°C, a solution of 5.0 g indole-3-carboxylic acid in 30 mL of N,N-dimethylformamide was dripped and stirred for 1 hr at 0°C. Then 10.7 g of methyl iodide was dripped in and stirred for 2 hr at room temperature. The reaction solution was poured into ice water, and after rinsing with chloroform, was made weakly acidic by the addition of 10% HCl to the aqueous layer. Extraction with ethyl acetate was performed, and after dehydration with anhydrous magnesium sulfate and filtration, the ethyl acetate was distilled off under vacuum. Purification was performed by silica gel column chromatography, n-hexane was added to the chloroform extract to precipitate crystals, and the crystals were filtered and rinsed with n-hexane to obtain 3.2 g of 1-ethylindole-3-carboxylic acid as white crystals.

Melting point: 145-147°C.

EXAMPLE 1

N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide

A suspension of 1.00 g of 1-methylindole-3-carboxylic acid was suspended in 10 mL of chloroform, and while stirring at room temperature, a solution of 6.00 g oxalyl chloride in 10 mL chloroform was dripped in, and the mixture was heated and refluxed for 1.5 hr. The chloroform and excess oxalyl chloride were distilled off under vacuum to obtain 1-methylindole-3-carboxylic acid chloride.

A mixture of 0.92 g 1-azabicyclo-[2,2,2,]-oct-3-yl amine hydrochloride, 1.91 g potassium carbonate, 20 mL water and 30 mL chloroform was prepared, and while stirring at 0°C, a solution of the above acid chloride in 10 mL chloroform was dripped in and stirred at 0°C for 4 hr. The reaction mixture was rinsed with water, the chloroform layer was dehydrated with anhydrous magnesium sulfate and filtered, and the chloroform was distilled off under vacuum. The residue was purified by alumina column chromatography, and then ether was added to the chloroform-methanol (97:3) eluate to precipitate the crystals. The crystals were filtered and rinsed with ether to obtain 0.33 g of N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide as white crystals.

Melting point: 202-203°C
Elemental analysis: ($C_{17}H_{21}N_3O$)
Theoretical value (%): C 72.57, H 7.47, N 14.83
Measured value (%): C 72.77, H 7.66, N 14.54

EXAMPLE 2

N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide hydrochloride

A solution of 0.30 g N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide in 10 mL ethanol was prepared, and after adding 10 mL of 10% HCl in ethanol, the ethanol was distilled off under vacuum. The residue was recrystallized from ethanol to obtain 0.17 g of N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide.

Melting point: 312-313°C
Elemental analysis: ($C_{17}H_{21}N_3O \cdot HCl$)
Theoretical value (%): C 63.84, H 6.93, N 13.14
Measured value (%): C 63.61, H 7.01, N 13.15

EXAMPLE 3

N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-ethylindole-3-carboxyamide

A suspension of 1.00 g of 1-ethylindole-3-carboxylic acid was suspended in 10 mL of chloroform, and while stirring at room temperature, a solution of 6.00 g oxalyl chloride in 10 mL chloroform was dripped in, and the mixture was heated and refluxed for 4 hr. The chloroform and excess oxalyl chloride were distilled off under vacuum to obtain 1-ethylindole-3-carboxylic acid chloride.

A mixture of 0.85 g 1-azabicyclo-[2,2,2,]-oct-3-yl amine hydrochloride, 1.76 g potassium carbonate, 3 mL water and 20 mL chloroform was prepared, and while stirring at 0°C, a solution

of the above acid chloride in 10 mL chloroform was dripped in. The reaction mixture was gradually warmed to room temperature and stirred for 3 hr. The reaction mixture was rinsed with water, the chloroform layer was dehydrated with anhydrous magnesium sulfate and filtered, and the chloroform was distilled off under vacuum. The residue was purified by alumina column chromatography, and then ether was added to the chloroform-methanol (97:3) eluate to precipitate the crystals. The crystals were filtered and rinsed with ether to obtain 0.22 g of N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-ethylindole-3-carboxyamide as white crystals.

Melting point: 185-187°C
Elemental analysis: ($C_{18}H_{23}N_3O$)
Theoretical value (%): C 72.70, H 7.80, N 14.13
Measured value (%): C 72.52, H 8.04, N 13.85

EXAMPLE 4

N-(1-azabicyclo-[2,2,2]-oct-3-yl) indole-3-carboxyamide

A reaction mixture was prepared by adding 15 mL of thionyl chloride to 1.0 g of indole-3-carboxylic acid and stirring at room temperature for 16 hr. The excess thionyl chloride was distilled off under vacuum to obtain indole-3-carboxylic acid chloride.

A mixture of 1.23 g 1-azabicyclo-[2,2,2,]-oct-3-yl amine hydrochloride, 2.57 g potassium carbonate, 50 mL water and 30 mL chloroform was prepared, and while stirring at 0°C, a solution of the above acid chloride in 10 mL chloroform was dripped in. The reaction mixture was gradually warmed to room temperature and stirred for 2 hr. After the aqueous layer was saturated with NaCl, separation was performed and the aqueous layer was further extracted with chloroform. The chloroform layers were combined and dehydrated with anhydrous magnesium sulfate and filtered, and the chloroform was distilled off under vacuum.

The residue was purified by alumina column chromatography, and isopropyl ether was added to the chloroform-methanol (8:2) eluate to precipitate the crystals. The crystals were filtered and rinsed with isopropyl ether to obtain 0.22 g of N-(1-azabicyclo-[2,2,2]-oct-3-yl) indole-3-carboxyamide as white crystals.

Melting point: 267-270°C
Elemental analysis: ($C_{16}H_{19}N_3O$)
Theoretical value (%): C 71.35, H 7.11, N 15.60
Measured value (%): C 71.32, H 6.94, N 15.30

EXAMPLE 5

(S)-(-)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide hydrochloride

A suspension of 5 g of 1-methylindole-3-carboxylic acid in 30 mL acetonitrile was prepared, and while cooling with ice water, 6.5 g of N,N'-dicyclohexylcarbodiimide and 4.8 g of 1-hydroxybenzotriazole hydrate were added and stirred for 2 hr.

Next, 3.5 g of (S)-(-)-1-azabicyclo-[2,2,2]-oct-3-yl amine was added and the mixture was stirred for 2 hr while cooling with ice water and an additional 20 min at room temperature. The reaction mixture was filtered to remove impurities and the solvent was distilled off. Dilute HCl was added to the residue to dissolve it, and the solution was rinsed with ethyl acetate. The aqueous layer

was neutralized with NaOH, extracted with chloroform, rinsed with water, dried with anhydrous magnesium sulfate, filtered, and the chloroform was distilled off under vacuum. The remaining crystals were dissolved in ethanol, a solution of 10% HCl in ethanol was added to form the hydrochloride, ether was added, and the precipitated crystals were filtered and recrystallized from isopropyl alcohol to obtain 5.85 g of (S)-(-)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide hydrochloride as white crystals.

Melting point: 199.5-202°C
Elemental analysis: ($C_{17}H_{21}N_3O \cdot HCl$)
Theoretical value (%): C 63.84, H 6.93, N 13.14
Measured value (%): C 63.59, H 7.10, N 13.20
$[\alpha]_D^{20}$ = -15.6 (c=1, H_2O)

EXAMPLE 6

(R)-(-)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-1-methylindole-3-carboxyamide hydrochloride

This compound was prepared in the same manner as Example 5 using (R)-(-)-1-azabicyclo-[2,2,2]-oct-3-yl amine.

Melting point: 198-202°C
Elemental analysis: ($C_{17}H_{21}N_3O \cdot HCl$)
Theoretical value (%): C 63.84, H 6.93, N 13.14
Measured value (%): C 63.60, H 7.11, N 13.01
$[\alpha]_D^{20}$ = +15.2 (c=1, H_2O)

(Rest of page intentionally left blank)

EXPERIMENTAL EXAMPLES

The following pharmacological tests results show the usefulness of representative examples of the inventive compounds.

Test Method

1. Bezold-Jarisch Reflex Inhibition

The effect of the test substance on the Bezold-Jarisch reflex in 5-7 week old male mice was investigated according to the procedure of Richardson et al (Richardson, B. P., Nature, Vol. 316, pp. 126-131, 1985). Under urethane anesthesia the animals were restrained in the supine position and changes in heart rate were recorded after an injection of 0.25 mg/kg serotonin via the caudal vein. When the heart rate after serotonin injection did not drop to 60% or less of the heart rate prior to injection because of pretreatment by the test substance, the test substance was judged to have an inhibitory effect on the Bezold-Jarisch reflex (positive). The ED_{50} was determined using a probit procedure from the positive rates in each test group at each dose. The test substance was administered by intraperitoneal injection 15 min prior to the serotonin injection. Table 1 shows the results.

(Rest of page intentionally left blank)

Table 1

Test Substance	No. of animals with reflex inhibition/number of animals tested Dose (mg/kg)							ED_{50} Mg/kg
	$3x10^{-5}$	$5x10^{-5}$	$1x10^{-2}$	$3x10^{-2}$	$5x10^{-2}$	$1x10^{-1}$	$3x10^{-1}$	
GR-38032F	---	---	0/5	3/7	4/5	5/6	5/5	0.036
ICS-205930	---	1/5	2/7	5/5	---	---	---	0.011
Compound from Example 1	1/5	4/5	5/5	---	---	---	---	0.004
Compound from Example 3	1/5	1/7	5/5	---	---	---	---	0.004

As can be clearly seen from Table 1, the compounds from Example 1 and Example 3 showed a much stronger inhibition of the Bezold-Jarisch reflex than the control substances.

The duration of this effect following a 0.1 mg/kg intraperitoneal injection of the test substance was investigated, and the results are shown in Table 2.

(Rest of page intentionally left blank)

Table 2

Test Substance	No. of animals with reflex inhibition/number of animals tested Time of pretreatment before serotonin injection (hr)				
	0.5	1	2	3	4
GR-38032F	1/4	1/5	---	---	---
ICS-205930	2/3	3/3	2/3	1/3	
Compound from Example 1	3/3	3/3	3/3	3/3	1/3
Compound from Example 3	3/3	3/3	3/3	4/4	0/3

As can clearly be seen from Table 2, the duration of the anti-serotonin effect of the compounds from Example 1 and Example 3 were much longer than that of the control substances.

2. Inhibition of Cisplatin-Induced Vomiting

Tests were performed according to the procedure of Cohen et al (Cohen, M. L., et al, J. Pharmacol. Exp. Ther. Vol. 248, 197-201, 1989). In these tests, male and female beagles weighing 7-12 kg were used. A dose of 2 mg/kg cisplatin was injected intravenously and for the next 6 hr the animals were observed for nausea and vomiting. The test substance was injected intramuscularly at two different times, 30 min and 90 min prior to the cisplatin injection.

Table 3A shows the results. The average value of the elapsed time before the emergence of vomiting was calculated only for the animals that vomited, and the average number of vomiting events was calculated for all animals tested.

Table 3A

Test Substance	Dose mg/kg	No. of vomiting animals/number of animals used	Elapsed time until vomiting (min)	No. of vomiting events (times)
Control	---	3/3	122.7±12.7	13.7±1.3
GR-38032F	0.1	2/2	236.5±28.5	6.0±4.0
ICS-205930	0.1	0/2	---	0.0±0.0
	0.01	3/4	191.3±18.3	5.3±2.8
Compound from Example 1	0.1	0/2	---	0.0±0.0
	0.01	4/4	260.0±28.0	1.0±0.0
Compound from Example 3	0.01	3/4	219.3±3.8	3.8±3.1
Compound from Example 4	0.1	0/2	---	0.0±0.0
	0.01	4/4	196.3±26.8	3.5±1.3

Similar observations were made when the test substance was injected intravenously 5 min prior to the administration of cisplatin (2 mg/kg, i.v.). Table 3B shows the results.

(Rest of page intentionally left blank)

Table 3B

Test Substance	Dose mg/kg	No. of vomiting animals/number of animals used	Elapsed time until vomiting (min)	No. of vomiting events (times)
Control	---	13/13	110.9±7.6	12.9±1.0
GR-38032F	0.1	5/5	171.0±8.2	10.4±1.4
	0.3	3/5	258.3±11.5	1.2±0.7**
	1	0/4		0±**
ICS-205930	0.01	4/4	140.8±3.6	14.0±1.8
	0.03	4/4	139.8±13.2	9.5±1.3
	0.1	3/4	192.7±36.7	1.8±0.9**
BRL-43694	0.01	4/4	144.8±5.5	9.5±1.7
	0.03	4/4	158.0±5.0	7.3±1.6*
	0.1	1/4	219.0	0.8±0.8**
Metoclopramide	0.1	4/4	121.8±6.9	14.0±1.2
	1	4/4	148.0±12.3	13.3±1.8
	3	4/4	181.5±12.5	4.3±1.1
Compound from Example 2	0.003	5/5	135.0±6.7	11.8±2.0
	0.01	4/5	151.0±9.7	5.4±1.7**
	0.03	3/5	205.0±31.8	1.2±0.6**
	0.1	0/4		0±**

(*: $p<0.05$, **: $p<0.01$)

As can clearly be seen from Tables 3A and 3B, A dose of 0.1 mg/kg of the inventive compound completely inhibited cisplatin-induced vomiting in all animals for a 6-hour period. Even a dose of 0.01 mg/kg delayed the time until the emergence of cisplatin-induced vomiting and decreased the number of vomiting events.

3. Emetic Effect

Male and female beagles (4 animals) were injected intravenously with the test substance to check for the presence or absence of vomiting.

At a dose of 5 mg/kg no vomiting was observed in any of the animals with the compound from Example 2, but at 10 mg/kg vomiting was observed in all animals.

4. Acute Toxicity

Six-week-old male mice (4 per group) were fasted overnight and then injected intraperitoneally with the test substance suspended in 0.5% methylcellulose solution. Survival was monitored for 48 hr after administration of the test substance, and the results are shown in Table 4A.

Table 4A

Test Substance	No. of animal deaths/number of animals tested Dose (mg/kg)			
	3	10	30	100
GR-38032F	0/4	3/4	4/4	---
ICS205930	---	---	0/4	1/4
Compound from Example 1	---	---	---	0/4
Compound from Example 3	---	---	---	0/4
Compound from Example 4	---	---	0/4	1/4

As can clearly be seen from Table 4A, no animal deaths were found with the compounds from Example 1 and Example 3 at doses of 100 mg/kg. On the other hand, 1 of 4 animals died with a 100 mg/kg dose of ICS-205930, and 3 of 4 animals died with a 10 mg/kg dose of GR-38032F The safety of the inventive compounds is thus clearly demonstrated.

The same observations were performed in 6-week-old male rats (SCL-SD, 4 per group) with intravenous injections (non-fasting) and oral doses of the test substance. The results are shown in Tables 4B and 4C.

Table 4B Intravenous Injection (No. of animal deaths/number of animals tested)

Test Substance	Dose (mg/kg)										
	10	18	20	22	24	30	40	100	110	120	130
ICS-205930						1/4	4/4				
BRL-43694		0/4	2/4	3/4	4/4						
GR-38032F	0/4					3/4					
Compound from Ex. 2								1/4	2/4	2/4	4/4

From the results shown in Table 4B the LD_{50} of BRL-43694 is 20.48 mg/kg, and the LD_{50} of the inventive compound (compound from Example 2) is 111.37 mg/kg.

Table 4C Oral Administration (No. of animal deaths/number of animals tested)

Test Substance	Dose (mg/kg)				
	100	200	400	2000	4000
ICS-205930	0/4	3/4	4/4		
Compound from Ex. 2				2/4	4/4

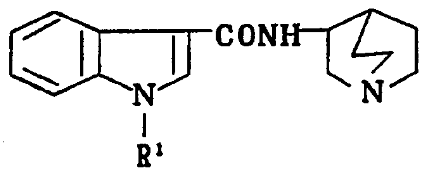
Industrial Applicability of the invention

The inventive compound shows excellent serotonin antagonism and demonstrates an antiemetic action. The opposing emetic effect emerged at doses of 500-1000 times the dose at which the antiemetic effect was observed (0.01 mg/kg) and because the toxicity of the inventive compound is low, it has a very wide range of safety.

The inventive compound has an excellent effect not found in current medicines, and because it has low toxicity, it can be used to suppress the nausea and vomiting induced by anticancer drugs. In addition, it can safely be used as an agent for regulating gastrointestinal peristalsis, an agent for the treatment of migraine headaches, an antipsychotic agent, and an antianxiety agent based on its serotonin antagonism.

Claims

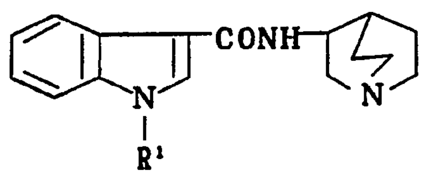
(1) The indole carboxamide derivative represented by General Formula [I] and its pharmacologically acceptable salts,



[I]

wherein, R^1 represents a hydrogen atom or alkyl group.

(2) A serotonin antagonist having as its main constituent the indole carboxamide derivative represented by General Formula [I] and its pharmacologically acceptable salts,



[I]

wherein, R^1 represents a hydrogen atom or alkyl group.

Translation Coordination Services
Lgt\TCS633
8/24/01
Stroman

THIS PAGE BLANK (USPTO)